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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,129	KAUHANEN ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/14/04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *1004*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Upon further consideration, the suggested examiner's amendment and indication of allowable subject matter previously agreed upon in the interview 10/21/01 (see enclosed paper) is hereby WITHDRAWN. Likewise, the statement of allowable subject matter set forth in the previous office action is hereby WITHDRAWN. This office action sets forth new grounds of rejection.

2. Applicant's amendments filed 9/14/04 have been entered. Claims 1-3 and 10 are pending. Applicant's arguments have been carefully considered but are not persuasive. The arguments are addressed following the statements of rejection.

Specification

3. The corrections to the specification have been entered. No objections to the specification remain.

4. This application is in compliance with the sequence rules.

5. The drawings filed 9/14/04 are approved.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3 and 10 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

The claims are drawn to methods for diagnosing a susceptibility for having a risk for development of alcoholism, wherein the method comprises a single step of detemining whether the person has a polymorphism in signal peptide part of the human preproNPY, wherein the polymorhism comprises a substitution of proline for leucine at position 7 in the signal peptide, said polymorphism being indicative of a risk for the development of alcoholism. The nature of the invention, thus, relies on an association between the presence of a polymorphic form of the human preproNPY wherein there is a proline at position 7 of the signal peptide and a risk for the development of alcoholism. The claim suggests that the person who has the proline at position 7 of the signal peptide of the human preproNPY have a greater likelihood of developing alcoholism than those that do not have this polymorphic form.

Furthermore, the nature of the invention is dependent upon the ability to detect the polymorphism itself.

Breadth of the Claims

The independent claim encompasses the detection of the polymorphism via any means in either a nucleic acid sample or a protein sample. Claim 3 specifically recites that the polymorphism is detected utilizing an antibody capable of binding the signal peptide part of the human preproNPY or a NPY peptide associated with any other cleavage product of said human preproNPY. Claims 2 and 10 are limited to analysis of nucleic acids.

State of the Art

The prior art teaches the detection of the polymorphism at position 7 in the signal peptide via analysis of nucleic acid sequence and that this polymorphism may be associated with seizures in alcohol withdrawal (see, for example, Okubu *et al.* as cited in the IDS). The prior art does not provide any suggestion or evidence to support an assertion that either allele of this polymorphism is associated with increased likelihood of developing alcoholism.

The prior art teaches that for men moderate drinking is defined as no more than two drinks per day, with a standard drink being 12 grams of pure alcohol (See for example, The Physician's Guide to Helping Patients with Alcohol Problems).

The prior art does not teach isolation and/or detection of the polymorphism via an antibody that differentiates the two alleles or via any other method. Neither the specification nor the prior art appear to provide the binding epitopes for the human preproNPY. There is no specific guidance given as to how to isolate the sample polypeptide (i.e. in which tissues expression might be high enough for a sample to be detected), and there are no examples of antibodies that are sufficient to discriminate between the alleles.

Teachings of the Specification and Working Examples

The experimental section of the specification describes a study in a cohort of men were questioned about their level of alcohol use and the average weekly consumption of alcohol was calculated for each subject. Further, the proportion of heavy users consisting of those whose average daily consumption exceeded 3 standard doses was calculated (p. 13, lines 15-25). The genotype of these men was determined using RFLP analysis (p. 14, lines 20-28). The proportion

of heavy drinkers in the genotype groups was compared using a chi-square test, with P-values less than 0.05 interpreted as being statistically significant (p. 15, lines 6-9).

The specification teaches that the proportion of heavy users was higher among men with the proline allele, but this difference was not a significant difference (p=0.10; p. 16, lines 5-8). Table II shows the alcohol consumption in grams of ethanol per week, and shows that the group of men with the proline allele had a higher mean weekly alcohol consumption in pure ethanol (115 g/wk versus 86 g/wk; p=0.03; p. 17). However, it is significant to note that even the level of alcohol consumption observed for the proline allele carriers falls within the defined level of "moderate drinkers" since an average of 115 g/week of alcohol averages to less than two drinks per day. The physician's guide includes this level of drinking as "low-risk drinking." Thus, while the specification demonstrates that there is a difference between the amount of alcohol consumed for proline allele carriers versus non-carriers, the specification fails to demonstrate a link between the allele and heavy drinking, high risk drinking or alcoholism.

There is no analysis in the specification of men or women who were diagnosed as alcoholics.

Furthermore, with regard to the scope of the claims which are directed towards analysis with antibodies or other means for detecting polymorphisms within polypeptides, specification teaches that the determination can be carried out as an immunoassay where a sample is contacted with an antibody capable of binding the signal peptide or a peptide associated with any other cleavage product of preproNPY (p. 6, lines 18-20). The specification generically teaches that antibodies can be raised against normal or mutated preproNPY utilizing in vivo or in vitro procedures. The specification does not exemplify such methods. Furthermore, the specification

does not exemplify any additional methods by which a polymorphism in a polypeptide itself can be detected. The specification does not teach isolation of the polypeptide from any biological sample from a patient or how to identify the polypeptide in a sample for assay for the polymorphism. Significantly, this polypeptide is a neuromodulator in the central nervous system. The specification does not provide any guidance as to specifically where or at what level the polypeptide is expressed within cells, a teaching that is significant for any method of detection which will detect polypeptide. Unlike the coding sequence of the polypeptide, which would be present in every cell in genomic DNA, the polypeptide may or may not be expressed in a given cell. There is no guidance in the specification as to how to determine even where this protein would be expressed in order to carry out the assays encompassed within the claimed invention.

Level of Unpredictability

The establishment of an association between a polymorphism and a give phenotype is an entirely empirical science, and indeed is highly unpredictable. The instant specification failed to show an association between heavy drinking and the polymorphism. The only association that was demonstrated showed that the mean alcohol consumption of Pro7 allele carriers was higher than that of non-carriers, but significantly, BOTH mean consumption levels were within the range of low risk consumption for men. An association observed in an initial study is frequently not supported in subsequent studies. This unpredictability is highlighted in the post filing date art concerning the putative association between the polymorphism of the instant application and alcoholism.

Ilveskoski et al. teach that the Pro7 allele might not predispose to alcoholism, but instead might retard the transition from social drinker to alcoholism (Alcoholism, clinical and experimental research, October 2001, 25(10) 1420-1422). Drube et al. screened 105 Japanese patients with alcoholism and did not find the polymorphisms within this population (Psychiatric Genetics, 2001, Vol. 11, No. 1, p. 53-55). This finding suggests that even if an association exists, it would not have predictive value in all populations. It is not a priori possible to predict which populations such a finding would be relevant for. Lappalainen et al. report that the frequency of the Pro7 allele was significantly higher in alcohol-dependent samples than in controls (Archives of General Psychiatry, September 2002, p. 825-831; see p. 828). In a study to follow-up that of Lappalainen et al., Zhu et al. teach that Pro7 frequencies were not significantly different in alcoholic and control populations (Alcoholism, Clinical and Experimental Research, January 2003, Vol. 27, No. 1, p. 19-24). Further, they conducted a meta-analysis wherein they found that the Pro7 frequency was the same in Caucasian alcoholics and Caucasian controls. Zhu et al. conclude that Pro7 is not associated with diagnosis of alcoholism in Caucasian populations. These studies demonstrate the high degree of unpredictability with regard to determining an association between this allele and alcoholism in particular. Even many years after the instant invention, there is no clear answer in the literature as to whether carrying the Pro7 allele results in an increased predisposition for development of alcoholism.

Further, is unpredictable whether the amino acid change in the seventh position of the signal sequence would be sufficient to result in the production of antibodies that can differentiate between the two molecules. In some cases, an antibody elicited by one antigen can cross-react

with a different antigen if the two different antigens share an identical or very similar epitope (Glodsby *et al.*, 2003, p. 141). Thus, absent knowledge of the binding epitopes and the effects of the instant polymorphism on those epitopes, it is difficult to predict whether or not any generated antibody will be able to function to differentiate the two alleles in an assay. In the instant case, it is unpredictable as to whether or not an antibody would be able to differentiate between the two variants, a feature that is essential for the practice of the claimed invention.

Conclusion

The instant specification does not provide any evidence which definitely demonstrates that carriers of the proline allele would have a higher likelihood of becoming alcoholics. The specification only demonstrates that carriers of the allele have an increased likelihood of consuming alcohol at a mean level that is higher than non-carriers, but both levels are low risk levels.

Thus, having considered all of these factors, particularly the absence of working examples, teaching in the specification and prior art, and high degree of unpredictability, it is concluded that it would require undue experimentation to practice the claimed invention.

Response to Remarks

The enablement rejection has been modified, but still includes portions that address the lack of enablement with regard to the detection of the polymorphism using antibody analysis or other polypeptide analysis. Applicant argues that the specification need not disclose what is well-known in the art. However, neither the specification nor the prior art appear to establish that antibodies which distinguish the polymorphism recited in the instant claims are well known in the art. Attorney arguments do not substitute for evidence on the record (see MPEP

716.01(c)). Applicant characterizes the examiner's rejection as a "contention, without scientific reasons or evidence." In the instant case, scientific reasons are set forth to support the conclusion. Namely, in order for an antibody to distinguish between two alleles, the change in the polypeptide must be sufficient so as to overcome any potential cross-reactivity, for example, it must be within a binding domain. It is not clear that this is the case in the instant methods. Again, applicant has provided no evidence to clarify the record on tis point. Applicant argues that it would not require undue experimentation to identify and develop monoclonal antibodies against epitopes of an altered preproNPY, however, as stated, though there is a single change in the encoded polypeptide, it is not clear a binding epitope would be modified so that it would be sufficient to raise discriminatory antibodies.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Juliet C. Switzer
Examiner
Art Unit 1634

October 29, 2004